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(54) **METHOD AND FORMULATION FOR TREATING RESISTANCE TO ANTIHYPERTENSIVES AND RELATED CONDITIONS**

METHODE UND ZUSAMMENSETZUNG ZUR BEHANDLUNG VON RESISTENZ GEGEN ANTIHYPERTENSIVA UND VERWANDTEN ZUSTÄNDEN

METHODE ET FORMULATION PERMETTANT DE TRAITER UNE RESISTANCE AUX ANTIHYPERTENSEURS ET DES AFFECTIONS ASSOCIEES

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Description

FIELD AND BACKGROUND OF THE INVENTION

[0001] The present invention relates to a method and pharmaceutical formulation for treating a patient who is resistant to the antihypertensive effect of an antihypertensive compound in absence of melatonin, a method for lowering nocturnal blood pressure in patients who have an abnormal rhythm in blood pressure in the absence or presence of an antihypertensive compound, a method for lowering cortisol levels and protecting from cardiovascular events, and use of melatonin in the manufacture of medicaments for the stated purposes.

[0002] There is a daily variation in blood pressure (circadian blood pressure rhythm) which is characterized by a nocturnal fall and a diurnal rise. The normal pattern of circadian blood pressure rhythm is reversed in elderly people and in those with Cushing's syndrome, those undergoing glucocorticoid treatment, and those with hyperthyroidism, central and/or peripheral autonomic dysfunction (Shy-Drager syndrome, tetraplegia, diabetic or uremic neuropathy etc.), chronic renal failure, renal or cardiac transplantation, congestive heart failure, eclampsia, sleep apnea syndrome, malignant hypertension, systemic atherosclerosis, accelerated hypertensive organ damage (Imai, Abe et al. Journal of hypertension (supplement) 8:S125-132, 1990) and fatal familial insomnia (Portaluppi, Cortelli et al. Hypertension 23:569-576, 1994). A less-than-normal decline in nocturnal blood pressure is seen in some hypertensive patients despite treatment with antihypertensive drugs. A less-than-normal decline in nocturnal blood pressure has been associated with excessive cardiovascular complications in hypertensive patients. Patients with impaired nocturnal blood pressure reduction (non-dippers) are at increased risk of developing target organ damage (1-4) and nondipper women have been shown to develop more cardiovascular events (5) than their dipper counterparts. The mechanism of the normal fall of blood pressure during sleep and the pathophysiological mechanisms responsible for lack of nocturnal fall in blood pressure remain to be fully elucidated.

[0003] Glucocorticoid hormones play a critical role in a variety of bodily functions. In the basal state, glucocorticoids exert a permissive effect on diverse body functions such as maintenance of blood pressure, euglycemia, and electrolyte and water hemostasis. In humans, cortisol is essential for life. Normally, cortisol secretion from the adrenal gland is rhythmic, with maximal blood levels in the early morning hours, and a decline to half of the peak value in the afternoon. During stress, excretion of cortisol is greatly increased to cope with serious whole body insult. However, sustained elevation of cortisol in circulation has detrimental effects on the immune system and on the ability of the body to cope with stress and disease. Most importantly, corticosteroids can provoke a neurodegenerative process in the hippocampus leading to impaired memory and cognitive functions. Prolonged exposure of the brain to corticosteroids makes it more vulnerable to degeneration induced by ischemia and epilepsy (McEwen, Annals of the New York Academy of Science, 1994, 746: 145-154). With aging, the basal secretion of cortisol increases by unknown mechanisms and its peak occurs earlier in the morning than in young adults (Moreley and Korenman, eds., Blackwell Scientific Publications, 1992, pp. 70-91). In addition, nocturnal cortisol levels have been found to be higher in coronary patients than aged-matched healthy subjects (Brugger and Herold, Biological Rhythm Research, 1995, 26: 373). There is an association between hypertension and high urine cortisol values (Lichtenfeld, Hunt et al, Hypertension, 31:569-74, 1998), oral cortisol increases blood pressure in a dose dependent manner (Kelly, Mangos et al, Clin Exp Pharmacol Physiol Suppl 25:S51-6, 1998). It has not been previously suggested that there is an association between the high cortisol levels and the absence of nocturnal dip in blood pressure.

[0004] Melatonin, the hormone secreted at night from the pineal gland, reaches its peak levels before the onset of the cortisol peak in humans. The production of melatonin declines with age. Also, nocturnal melatonin levels are lower in coronary patients than in healthy aged-matched individuals. However, it has not been suggested that melatonin affects cortisol secretion under normal conditions.

Cardiovascular effects of conventional release melatonin

[0005] Melatonin, the hormone of the pineal gland, is normally secreted at night and plays a role in the biologic regulation of circadian rhythms, including sleep (Brzezinski, N Engl J Med 1997; 336: 186-195, Penev and Zee, Ann Neurol 1997; 42: 545-553). Vasorelaxing action of melatonin (at high concentrations 10-1000 μM) has been observed in rabbit aorta in vitro (Satake et al., Gen. Pharmacol., 1991, 22: 219-221, and 22:1127-1133).

[0006] Rodent studies indicate the presence of melatonin receptors in some arterial vessels and it's ability to modulate rat vascular smooth muscle tone (Capsoni et al, Neuroreport 1995; 6: 1346-1348, Mahle et al, J Biol Rhythms 1997; 12: 690-696). This modulation may be manifested as vasodilatation or vasoconstriction depending on the animal species.

[0007] The effects of melatonin on blood pressure and on the human cardiovascular system is complex (Lusardi et al, Blood Press Monit 1997; 2: 99-103, Cagnacci et al,1998; 274: 335-338, Arangino et al, Am J Cardiol 1999; 83: 1417-1419; Terzolo et al. J. Pineal Research, 1990, 9: 113-124). Bedtime melatonin ingestion (5 mg) for 4 weeks to young normotensive subjects caused a decrease in systolic blood pressure throughout the 24 h period, a decrease in

diastolic blood pressure limited to the second half of the night, a slight lowering of the heart rate during the diurnal hours, and an acceleration during the second half of the night (Lusardi et al, Blood Press Monit 1997; 2: 99-103). The daytime administration of melatonin (1 mg) to young women or men reduced the systolic and diastolic blood pressure within 90 min after administration Cagnacci et al, 1998; 274: 335-338; Arangino et al, Am J Cardiol 1999; 83: 1417-1419)). The administration of melatonin at 08:00 to aged postmenopausal women surprisingly increases their cortisol levels (Cagnacci, Soldani and Yen, L Pineal Res, 22:81-5, 1997).

[0008] The effects of long-term (2 months), low dose (2 mg/os daily), time specified (18:00 h) melatonin administration on endocrine and cardiovascular variables in adult men have also been studied by Terzolo et al. (J. Pineal Research, 1990, 9: 113-124). After treatment, a marked elevation of mean serum melatonin levels were recorded, with a significant advance of its circadian rhythm. The 24 h patterns of cortisol and testosterone displayed an anticipation of the morning acrophases at about 1.5 h (not significant) for cortisol and 3 h (significant) for testosterone. Prolactin pattern was unchanged as well as serum levels of triiodothyronine and thyroxine. Likewise, the response of luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, thyroid stimulation hormone (TSH) cortisol, adrenocorticotrophin (ACTH) and aldosterone to a stimulation test with gonadotropin releasing hormone (GNRH) thyrotropin releasing hormone (TRH), adrenocorticotrophin (ACTH) and testosterone to human chorionic gonadotrophin (HCG) were also unaffected. The circadian organization of the cardiovascular variables, i.e. systolic and diastolic blood pressure, heart rate, did not show any changes after melatonin treatment.

[0009] It is an object of the present invention to the lower cortisol level in humans and particularly to defer the peak of cortisol in the human cortisol profile. It is a further object of the invention to lower the blood pressure of a patient who is resistant to the antihypertensive effect of an antihypertensive compound in absence of melatonin, and especially to lower the nocturnal blood pressure in non-dippers. It is believed that these objects will potentially contribute to decrease in blood pressure, prevention of ischemic attacks and provide prophylactic protection against the detrimental effects of ischemia on the heart. Other objects of the invention will be apparent from the description which follows.

[0010] In U.S. Patent No. 5,700,828, there is described a method for treating or minimizing anoxic or ischemic brain injuries, by administering melatonin to a mammal suffering from an anoxic or ischemic insult, this being defined as a trauma that causes a lack of blood flow to the brain and/or a lack of oxygen to the brain. This patent does not suggest that melatonin might prevent or ameliorate the anoxic or ischemic insult, per se.

[0011] In U.S. Patent No. 5,849,338, filed August 26, 1997, there is described a unit dosage form for treating vasoconstriction and physiological conditions giving rise to it, comprising, in brief, Mg, vitamins C and E, folic acid, Se and melatonin. Melatonin is included only because of certain of its properties which were known at the filing date and which are described in this patent.

[0012] European patent 0518 468 describes a pharmaceutical controlled-release formulation comprising melatonin in combination with at least one pharmaceutical carrier, diluent or coating, and adapted to release melatonin over a predetermined time period, according to a profile which, taking into account the existing profile, simulates the profile in plasma of a human having a normal endogenous melatonin profile. It also describes use in the manufacture of a medicament for therapeutic application in the prevention of sudden infant death syndrome in infants, of a formulation which comprises melatonin in combination with at least one diluent, carrier, coating or adjuvant. In another aspect of the invention, the controlled release medicament may take the form of a pharmaceutical formulation, which includes at least one of the following additional components (α) and (β): (α) at least one carrier, diluent or adjuvant; (β) at least one antihypertensive compound in an amount effective to exert a blood pressure lowering effect in a patient requiring such treatment; and is additionally characterized by at least one of the following features:

(i) It is adapted for oral, rectal, parenteral or transdermal administration;
(ii) it is in unit dosage form, each unit dosage comprising an amount of melatonin which lies within the range of 2.5-20 mg;
(iii) it is adapted to release melatonin at a predetermined controlled rate;
(iv) it comprises also at least one melatonin receptor modifier and/or melatonin profile modifier;
(v) said carrier, diluent or adjuvant includes at least one acrylic resin.

SUMMARY OF THE INVENTION

[0013] The above objects may be achieved by the present invention, which in one aspect provides use of melatonin in the manufacture of a controlled release medicament, for the prevention or treatment of symptoms of hypertension in a patient who is resistant to the antihypertensive effect of an antihypertensive compound administered in absence of melatonin. The medicament may be a pharmaceutical formulation which comprises, in addition to at least one carrier, diluent or adjuvant:

melatonin in an amount effective to ameliorate or prevent symptoms of hypertension developing in a patient who is

resistant to the antihypertensive effect of an antihypertensive compound administered in absence of melatonin; at least one antihypertensive compound in an amount effective to exert an antihypertensive effect in presence of melatonin, in a patient requiring such treatment. Said use is particularly applicable wherein said patient is a non-dipper and/or exhibits a morning rise in blood pressure, despite use of antihypertensive drugs. The medicament above finds use in a method for the prevention or treatment of symptoms of hypertension in a patient who is resistant to the antihypertensive effect of an antihypertensive compound administered in absence of melatonin, which comprises administering melatonin to such patient, in an amount effective to ameliorate or prevent symptoms of hypertension developing in the patient.

[0014] According to another aspect, the invention provides use of melatonin in the manufacture of a medicament for imparting in a patient at least one effect selected from improvement in mood and daytime vigilance, modifying the 24-hour cortisol profile by both reduction of the 24-hour average cortisol level and delaying the 24-hour peak level of.cortisol in the patient, and prophylactic protection against cardiac ischemia, the medicament being a controlled release pharmaceutical formulation adapted for oral administration, which comprises melatonin in an amount effective to impart at least one of the above-stated effects. Such a medicament may impart in a patient at least one effect selected from improvement in mood and daytime vigilance, postponement of the peak level of cortisol in the patient and potential prophylactic protection against the detrimental effects of ischemia on the heart, the medicament being a pharmaceutical formulation which comprises melatonin in an amount effective to impart at least one of the above-stated effects.

[0015] The medicament above finds use in a method for imparting in a patient at least one effect selected from improvement in mood and daytime vigilance, postponement of the peak level of cortisol in the patient and potential prophylactic protection against the detrimental effects of ischemia on the heart, which comprises administering to the patient melatonin in an amount and in a manner effective to achieve said at least one effect.

[0016] The expression "improvement in mood" in the present context is intended to connote avoidance of mood depression which may be associated with administration of melatonin in conventional form, i.e. not in controlled release form.

[0017] Surprisingly, administration of melatonin to humans appears to lower excretions rates and diurnal variations. Also, there is a difference in this respect between controlled- and regular- release melatonin in that the controlled release form is able to change and delay the diurnal profile of cortisol whereas the regular form just suppresses but does not shift significantly the time of the peak.

DETAILED DESCRIPTION OF THE INVENTION

[0018] The medicament/pharmaceutical formulation may be administered in any convenient form, such as one adapted for oral, rectal, parenteral or transdermal administration. It may be e.g. in unit dosage form. The melatonin is in the form of a controlled release formulation, wherein the melatonin is preferably released at a predetermined controlled rate.

[0019] The at least one carrier, diluent or adjuvant may, for example, include at least one acrylic resin.

[0020] The amount of melatonin presently contemplated for use in preventing or treating hypertension will be the amount found to be effective for this purpose, presently believed to be, in the case of oral administration, more than 0.5 mg and no more than 100 mg daily, e.g. 0.5-50 mg, preferably 2.5-20 mg, and for parenteral or transdermal administration, between 0.1 and 50 mg. In accordance with the invention, an effective amount of melatonin may be formulated e.g. together with an effective dosage of a antihypertensive drug. Accordingly, in one aspect of the invention, the controlled release medicament may be in unit dosage form, each unit dosage comprising an amount of melatonin which lies within the range of 0.5-50 mg.

[0021] In another aspect of the invention, the controlled release medicament may take the form of a pharmaceutical formulation, which includes at least one of the following additional components (α) and (β): (α) at least one carrier, diluent or adjuvant; (β) at least one antihypertensive compound in an amount effective to exert a blood pressure lowering effect in a patient requiring such treatment; and is additionally characterized by at least one of the following features:

(i) It is adapted for oral, rectal, parenteral or transdermal administration;
(ii) it is in unit dosage form, each unit dosage comprising an amount of melatonin which lies within the range of 2.5-20 mg;
(iii) it is adapted to release melatonin at a predetermined controlled rate;
(iv) it comprises also at least one melatonin receptor modifier and/or melatonin profile modifier;
(v) said carrier, diluent or adjuvant includes at least one acrylic resin.

[0022] In a further aspect, the controlled release medicament may be adapted for oral, parenteral or transdermal administration, and may contain, in the case of oral administration, more than 0.5 mg and no more than 100 mg melatonin, and in the case of parenteral or transdermal administration between 0.1 and 50 mg. In this aspect, the controlled release

medicament may take the form of a pharmaceutical formulation which comprises in addition to melatonin, at least one carrier, diluent or adjuvant, and at least one antihypertensive compound in an amount effective to exert an antihypertensive effect in presence of melatonin, in a patient requiring such treatment.

[0023] In one aspect of the invention, the controlled release pharmaceutical formulation adapted for oral administration may be further characterized by at least one of the following features:

(i) it is adapted to release melatonin over a predetermined time period;
(ii) it is adapted to release melatonin according to a profile which simulates the nocturnal profile in plasma of a human having a normal endogenous melatonin nocturnal profile. In this aspect, the controlled release pharmaceutical formulation adapted for oral administration may be in particulate form comprising coated particles and the desired controlled release properties may be achieved by at least one of the following features, namely:

(a) by variation in the particle size of the melatonin;
(b) by use of at least two different coating materials which dissolve at different rates in the human body; and
(c) by varying the thickness of coating material(s) whereby the particulate melatonin is coated with different thicknesses of coating material(s) which dissolve at different rates in the human body. In particular, in this aspect, the controlled release pharmaceutical formulation adapted for oral administration may comprise particulate melatonin coated with at least one polymeric coating material.

[0024] In another aspect of the invention, the controlled release pharmaceutical formulation adapted for oral administration may comprises at least one additional medicament selected from benzodiazepine melatonin receptor modifiers, benzodiazepine melatonin profile modifiers, beta-blockers, calcium channel blockers and serotonin uptake inhibitors.

[0025] The controlled release pharmaceutical formulation adapted for oral administration may comprise also at least one melatonin receptor modifier and/or melatonin profile modifier.

[0026] Once the concept of the present invention for treatment or prevention of hypertension using melatonin is known according to the present invention, no inventive skill would be required to ascertain the range of effective amounts of melatonin for the present purpose, for various routes of administration. Where the pharmaceutical formulation includes at least one antihypertensive agent, this may for example be selected from Diltiazem, Captopril, Atenolol, Benazepril, Enalapril, Valsartan, Metoprolol, Terazosin, Prazosin, Minoxidil, Clonidine, Ramipril and pharmaceutically acceptable salts thereof. The daily dosage rates for oral administration of the exemplified hypertensive compounds, is shown in the following table:

Table 1: Antihypertensive Compounds

Compound	Daily Dosage (mg) possible	usual
Diltiazem HCl	180-300	240
Captopril	12.5-50	12.5
Atenolol	100	100
Benazepril HCl	5-20	10
Enalapril Maleate	5-20	10
Valsartan	80-160	80
Metoprolol tartarate	95-200	100
Terazosin HCl	1-10	1
Prazosin HCl 4-64	0.5-5	0.5-1
Minoxidil	5	5
Clonidine HCl	0.15	0.15
Ramipril	1.25-5	2.5

[0027] The invention will be illustrated by the following Examples.

Example 1

[0028] The following ingredients are mixed together and the mixture was compressed in a 7 mm cylindrical punch, at 2.5 tons, in order to make controlled release tablets: Captopril (12.5mg/tablet), melatonin (5 mg/tablet), and Eudragit™ RS 100 acrylic resin carrier (Rohm Pharma) and lactose in an approximately 1:1 ratio by weight. While this formulation

should be administered in accordance with a physicians instructions, it is presently contemplated that two such tablets taken two hours before bedtime would be appropriate.

Example 2

[0029] The following ingredients are mixed together and the mixture was compressed in a 7 mm cylindrical punch, at 2.5 tons, in order to make controlled release tablets: Diltiazem (180mg/tablet), melatonin (5 mg/tablet), and Eudragit™ RSPO acrylic resin carrier (Rohm Pharma), lactose and calcium hydrogen phosphate in an approximately 2:1:2.5 ratio by weight. While this formulation should be administered in accordance with a physicians instructions, it is presently contemplated that two such tablets taken two hours before bedtime would be appropriate.

Experiment 1

[0030] The effect of melatonin on blood pressure was determined on a trial population of 52 hypertensive and 130 normotensive elderly patients. All patients, who had been insomniacs, were diagnosed according to DSM IV. They consisted of 86 men and 96 women, age 72±9 years. In a randomized, double blind, subjects were given daily either 1, 2 or 5 mg melatonin in a controlled-release formulation (Circadin™, Neurim Pharmaceuticals, Israel), two hours before bedtime, or a placebo of identical appearance, for a period of 3 weeks. During the last week of the treatment period, BP was assessed at the morning and comparisons were made between placebo or melatonin treatments, and baseline. The results are shown in tables 2 and 3.

Table 2: results of Experiment 1

Hypertensive patients (>140 mm Hg Systolic BP at baseline)										
	Systolic baseline		Systolic Treatment			Diastolic baseline		Diastolic Treatment		
Dose	Average	SD	Average	SD	P value	Average	SD	Average	SD	Pvalue
0	149	5	146	11 1	0.24	83	6	85	6	0.62
1	145	7	137	9	0.05	82	4	79	3	0.09
2	147	8	132	9	0.000009	81	6	76	6	0.0064
5	144	5	137	11 1	0.04	82	7	81 1	6	0.97
Normotensive patients (<140 mm Hg Systolic BP at baseline)										
	Systolic baseline		Systolic Treatment			Diastolic baseline		Diastolic Treatment		
Dose	Average	SD	Average	SD	P value	Average	SD	Average	SD	Pvalue
0	120	11	123	13	0.14	74	7	75	6	0.42
1	121	10	126	16	0.11	75	7	75	9	0.71
2	122	13	124	15	0.69	75	7	74	8	0.59
5	121	12	124	14	0.16	75	8	76	9	0.55

Conclusions

[0031] Exogenous melatonin administration in the evening decreased daytime systolic and diastolic in hypertensive elderly subjects. Surprisingly, the administration of the controlled release formulation (1-5 mg) had no significant effect in normotensive subjects. It may be noted that antihypertensive drugs cause a decrease in blood pressure when administered to normotensive subjects and that administration of a regular release formulation of melatonin (5 mg) in the evening has been shown to lower blood pressure in young normotensive subjects throughout the 24 h period. (Lusardi et al, Blood Press Monit 1997; 2: 99-103).

Experiment 2

[0032] Sixteen elderly patients with essential hypertension were studied. Twenty-four hour ambulatory blood pressures were measured in all patients. Patients were defined as dippers (n = 8) or nondippers (n = 8) according to nocturnal fall in mean arterial pressure. 24-hours urine was collected in two collections, one during daytime, and one during nighttime.

Urinary excretion of the main melatonin metabolite 6-sulfatoxymelatonin (6SMT) was determined by ELISA assay in duplicates. Both groups were similar in regard to age and sex. Mean arterial pressure decreased by 10.2% during nighttime in the dippers and increased by 8% in the nondipper patients. Urinary 6SMT increased by 240% during sleep, from 3.28 ± 0.87 (units) during daytime to 8.19 ± 1.68 (units) during nighttime ($p < 0.05$) in the dippers, whereas it remained unchanged in the nondippers (2.31 ± 0.68 (units) during daytime and 2.56 ± 0.79 (units) during nighttime). Results are shown in table 3.

Table 3: results of Experiment 2

	Dippers (n=8)	Nondippers (n=8)
Day	3.28 ± 0.87	2.31 ± 0.68
Night	8.19 ± 1.68	2.56 ± 0.79

Conclusions

[0033] Nondipper hypertensive patients exhibit blunted nocturnal melatonin secretion. Thus, exogenous melatonin may play a role in the circadian rhythm of blood pressure.

Investigation of the effect of melatonin on cortisol profile and mood

[0034] The following experiments were performed in a double-blind, placebo controlled crossover fashion. Each patient received all three kinds of tablets (placebo, regular release and controlled release) but in random order not known to him or the staff.

Experiment 3

[0035] Administration of melatonin (2 mg) in a controlled release formulation (SR-Mf), once daily at 10 PM, for one week, to eight healthy elderly persons suffering from insomnia, resulted in a significant increase in their sleep efficiency but not sleep latency. (Sleep efficiency is the amount of time spent asleep from total time in bed; sleep latency is the time taken to fall asleep from first lights-off). On the other hand treatment of the same individuals with melatonin (2 mg) in a regular release formulation (RM) did not improve sleep efficiency but shortened sleep latency compared to placebo treatment of the same subjects. These results can be explained by the short half-life of melatonin in the blood. Namely, the controlled release formulation produces lower blood levels of the hormone for extended periods of time and thus its effects may start slowly but may be significant later on during the night.

[0036] The cortisol level in these patients was assessed by the urinary excretion of the hormone at 2 hours intervals over a 24 hour period. In the placebo treatment group, patients displayed a cortisol rhythm which reached its peak at 8: 36 AM and the cortisol then declined as is known for subjects above 40 years of age (see Sherman et al., Journal of Clinical Endocrinology and Metabolism 1985, 61: 439). The mean 24 hour excretion rate/hour (which approximated blood concentrations) of the cortisol in urine in the control group was 3.2 microgram/hour. The amplitude of the rhythm (i.e. maximal deviation of the mean 24 h to maximum or minimum excretion rate) was 1.8 μg/hour.

[0037] After treatment for 1 week with the regular release melatonin the overall amount of cortisol excreted was reduced. The mean 24 hour excretion rate decreased to 2.5 μg/hour and the amplitude decreased to 1.0 μg/hour. In addition there was a slight backwards shift in the time of the peak, which occurred at 8:27 AM. Anticipation of the cortisol rhythm after administration of regular release melatonin is compatible with observations made by Terzolo et al., J. Pineal Research, 1990, 9: 113-124. However, decrease in mean 24 hour levels and amplitude of the cortisol rhythm was not observed by Terzolo.

[0038] After one week's treatment with controlled release melatonin, it was found that like the regular melatonin, secretion of cortisol was attenuated (mean 24 h rate was 2.5 μg /hour) and the amplitude 1.2 μg/hour as with the regular release), but the peak was delayed significantly to later in the day and occurred at 12:06 PM. Thus, the peak was delayed by administration of controlled release melatonin instead of being the same or slightly advanced. The same cortisol profile was also found in these patients after 1 month's treatment with the controlled release formulation (mean 24 hour excretion 2.5 μg /hour, amplitude 1.0 μg /hour and peak time 12:08 hours).

Conclusions

[0039] These results show that the response of the body to melatonin is not obvious: the body reads the melatonin

profile and not just the fact that it is present at some time. Interestingly, in humans younger than 40 years, the cortisol rhythm is also delayed compared to older individuals (Sherman et al., *loc cit*). Hence, the cortisol profile generated in the elderly after the controlled release melatonin treatment is similar to that in younger individuals.

Discussion

[0040] It has recently been found that in coronary patients, melatonin at night is low whereas cortisol levels are high (Brugger and Herold, Biological Rhythm Research, 1995, 26: 373). It should be noted that cortisol is a stress hormone, and its high levels in the morning may be linked to the increased prevalence of heart attacks in the morning hours. The present experiment shows that administration of regular release melatonin can lower cortisol production but that administration of controlled release melatonin both lowers the cortisol level and delays its peak and thus can potentially lower the risk for an ischemic attack during the morning hours.

Experiment 4

[0041] This experiment was performed on 10 young healthy males age 26-30. They received one controlled-release (SR-M) or regular release (RM) tablet containing melatonin (2 mg) or placebo per day with one day washout between treatments. The tablets were taken at 11:00 AM and the subjects were asked to sleep between 12-15 hours. Mood was assessed by Lacer-Bond visual analog scale questionnaires before and after the sleep. The results indicated that regular melatonin (2 mg) significantly shortened nap sleep latency and increased sleep efficiency. The controlled release formulation also had similar effects. However, the regular release form produced feelings of hostility and sleepiness whereas the controlled release form had no negative effect on mood. These data also indicate that the effects of melatonin on mood depend on the profile generated. It should be noted that the lack of effect on mood cannot be explained by the lower concentrations of melatonin generated in he blood by the controlled release formulation since similar concentrations of melatonin (regular) have been shown by several studies to affect mood and sleepiness. Hence, both the timing and pattern of melatonin administration are important in affecting physiological parameters. The same dose given at different times or in different patterns may have different effects.

Claims

1. Use of melatonin in the manufacture of a controlled release medicament, for the prevention or treatment of symptoms of hypertension in a patient who is resistant to the antihypertensive effect of an antihypertensive compound administered in absence of melatonin.

2. Use according to claim 1, wherein said medicament is in unit dosage form, each unit dosage comprising an amount of melatonin which lies within the range of 0.5-50 mg.

3. Use according to claim 1, wherein said medicament takes the form of a pharmaceutical formulation, which includes at least one of the following additional components (α) and (β): (α) at least one carrier, diluent or adjuvant; (β) at least one antihypertensive compound in an amount effective to exert a blood pressure lowering effect in a patient requiring such treatment; and is additionally **characterized by** at least one of the following features:

   (i) It is adapted for oral, rectal, parenteral or transdermal administration;
   (ii) It is in unit dosage form, each unit dosage comprising an amount of melatonin which lies within the range of 2.5-20 mg;
   (iii) it is adapted to release melatonin at a predetermined controlled rate;
   (iv) it comprises also at least one melatonin receptor modifier and/or melatonin profile modifier;
   (v) said carrier, diluent or adjuvant includes at least one acrylic resin.

4. Use of melatonin in the manufacture of a medicament for imparting in a patient at least one effect selected from improvement in mood and daytime vigilance, modifying the 24-hour cortisol profile by both reduction of the 24-hour average cortisol level and delaying the 24-hour peak level of cortisol in the patient, and prophylactic protection against cardiac ischemia, the medicament being a controlled release pharmaceutical formulation adapted for oral administration, which comprises melatonin in an amount effective to impart at least one of the above-stated effects.

5. Use according to claim 4, wherein the formulation is further **characterized by** at least one of the following features:

(i) it is adapted to release melatonin over a predetermined time period;
(ii) it is adapted to release melatonin according to a profile which simulates the nocturnal profile in plasma of a human having a normal endogenous melatonin nocturnal profile.

6. Use according to claim 5, wherein the formulation is in particulate form comprising coated particles and the desired controlled release properties are achieved by at least one of the following features, namely:

(a) by variation in the particle size of the melatonin;
(b) by use of at least two different coating materials which dissolve at different rates in the human body; and
(c) by varying the thickness of coating material(s) whereby the particulate melatonin is coated with different thicknesses of coating material(s) which dissolve at different rates in the human body.

7. Use according to claim 6, wherein the formulation comprises particulate melatonin coated with at least one polymeric coating material.

8. Use according to claim 4, wherein the formulation comprises at least one additional ingredient selected from melatonin receptor modifiers and melatonin profile modifiers.

9. Use according to claim 8, wherein the formulation comprises at least one additional medicament selected from benzodiazepine melatonin receptor modifiers, benzodiazepine melatonin profile modifiers, beta-blockers, calcium channel blockers and serotonin uptake inhibitors.

10. Use of melatonin according to claim 1, wherein said patient is a non-dipper and/or exhibits a morning rise in blood pressure, despite use of antihypertensive drugs.

11. Use according to claim 1, wherein said medicament is adapted for oral, parenteral or transdermal administration, and contains, in the case of oral administration, more than 0.5 mg and no more than 100 mg melatonin, and in the case of parenteral or transdermal administration between 0.1 and 50 mg.

12. Use according to claim 11, where said medicament takes the form of a pharmaceutical formulation which comprises in addition to melatonin, at least one carrier, diluent or adjuvant, and at least one antihypertensive compound in an amount effective to exert an antihypertensive effect in presence of melatonin, in a patient requiring such treatment.

Patentansprüche

1. Verwendung von Melatonin zur Herstellung eines Medikaments mit kontrollierter Freisetzung zur Vorbeugung oder Behandlung von Symptomen von Hypertonie bei einem Patienten, der nicht auf die antihypertonische Wirkung einer antihypertonischen Verbindung anspricht, die in Abwesenheit von Melatonin verabreicht wird.

2. Verwendung gemäß Anspruch 1, wobei das Medikament in Form einer Dosiseinheit ist und jede Dosiseinheit eine Menge an Melatonin umfasst, die in dem Bereich von 0,5 - 50 mg liegt.

3. Verwendung gemäß Anspruch 1, wobei das Medikament die Form einer pharmazeutischen Formulierung annimmt, die mindestens einen der folgenden zusätzlichen Bestandteile (α) und (β) enthält: (α) mindestens einen Träger, ein Verdünnungsmittel oder einen Hilfsstoff; (β) mindestens eine antihypertonische Verbindung in einer Menge, um eine wirksame Blutdruck senkende Wirkung bei einem Patienten auszuüben, der eine derartige Behandlung benötigt; und ist zusätzlich durch mindestens eines der folgenden Merkmale charakterisiert:

(i) es ist angepasst für die orale, rektale, parenterale oder transdermale Verabreichung;
(ii) es ist in Form einer Dosiseinheit, wobei jede Dosiseinheit eine Menge an Melatonin umfasst, die in dem Bereich von 2,5 - 20 mg liegt;
(iii) es ist angepasst, um Melatonin mit einer vorbestimmten kontrollierten Geschwindigkeit freizusetzen;
(iv) es umfasst auch mindestens einen Melatoninrezeptor-Modifikator und/oder Melatoninprofil-Modifikator;
(v) der Träger, das Verdünnungsmittel oder der Hilfsstoff enthält mindestens ein Acrylharz.

4. Verwendung von Melatonin zur Herstellung eines Medikaments zur Vermittlung bei einem Patienten mindestens einer Wirkung, ausgewählt aus Verbesserung der Gemütsverfassung und Tageswachsamkeit, Modifikation des 24-

Stunden Cortisolprofils sowohl durch Reduktion des durchschnittlichen 24-Stunden Cortisollevels als auch durch Verzögerung des 24-Stunden Höchststandes von Cortisol bei dem Patienten, und prophylaktischer Schutz gegen Herzischämie, wobei das Medikament eine pharmazeutische Formulierung mit kontrollierter Freisetzung ist, angepasst für die orale Verabreichung, welches Melatonin in einer Menge umfasst, um mindestens eine der vorstehenden Wirkungen wirksam zu vermitteln.

5. Verwendung gemäß Anspruch 4, wobei die Formulierung ferner durch mindestens eines der folgenden Merkmale charakterisiert ist:

(i) sie ist angepasst, um Melatonin über eine vorbestimmte Zeitspanne freizusetzen;
(ii) sie ist angepasst, um Melatonin gemäß einem Profil abzugeben, das das nächtliche Profil im Plasma eines Menschen mit einem normalen, endogenen, nächtlichen Melatoninprofil simuliert.

6. Verwendung gemäß Anspruch 5, wobei die Formulierung partikelförmig ist, umfassend beschichtete Partikel, und die gewünschten Eigenschaften zur kontrollierten Freisetzung werden durch mindestens eines der folgenden Merkmale erreicht, nämlich:

(a) durch Variation der Partikelgröße des Melatonins;
(b) durch Verwendung von mindestens zwei unterschiedlichen Beschichtungsmaterialien, die im menschlichen Körper mit unterschiedlichen Geschwindigkeiten gelöst werden; und
(c) indem die Dicke des/der Beschichtungsmaterial(s/ien) variiert wird, wobei das partikuläre Melatonin mit unterschiedlichen Dicken von Beschichtungsmaterial(ien) beschichtet wird, das/die mit unterschiedlichen Geschwindigkeiten im menschlichen Körper gelöst werden.

7. Verwendung gemäß Anspruch 6, wobei die Formulierung partikuläres Melatonin umfasst, das mit mindestens einem polymeren Beschichtungsmaterial beschichtet ist.

8. Verwendung gemäß Anspruch 4, wobei die Formulierung mindestens einen zusätzlichen Inhaltsstoff umfasst, der ausgewählt wird aus Melatoninrezeptor-Modifikatoren und Melatoninprofil-Modifikatoren.

9. Verwendung gemäß Anspruch 8, wobei die Formulierung mindestens ein zusätzliches Medikament umfasst, das ausgewählt wird aus Benzodiazepin-Melatoninrezeptor-Modifikatoren, Benezodiazepin-Melatoninprofil-Modifikatoren, Beta-Blockern, Calciumkanal-Blockern und Hemmern der Serotoninaufnahme.

10. Verwendung von Melatonin gemäß Anspruch 1, wobei der Patient ein Patient mit verminderter nächtlicher Blutdruckabsenkung (non-dipper) ist und/oder einen morgendlichen Anstieg des Blutdrucks zeigt, trotz der Verwendung von antihypertonischen Arzneimitteln.

11. Verwendung gemäß Anspruch 1, wobei das Medikament für die orale, parenterale oder transdermale Verabreichung angepasst ist, und enthält im Fall der oralen Verabreichung mehr als 0,5 mg und nicht mehr als 100 mg Melatonin, und im Fall der parenteralen oder transdermalen Verabreichung zwischen 0,1 und 50 mg.

12. Verwendung gemäß Anspruch 11, wobei das Medikament die Form einer pharmazeutischen Formulierung annimmt, welche zusätzlich zu Melatonin mindestens einen Träger, ein Verdünnungsmittel oder einen Hilfsstoff umfasst, und mindestens eine antihypertonische Verbindung in einer Menge, um eine wirksame antihypertonische Wirkung in Gegenwart von Melatonin bei einem Patienten auszuüben, der eine derartige Behandlung benötigt.

Revendications

1. Utilisation de mélatonine pour la fabrication d'un médicament à libération contrôlée, destiné à la prévention ou au traitement de symptômes de l'hypertension chez un patient qui est résistant à l'effet anti-hypertenseur d'un composé anti-hypertenseur administré en l'absence de mélatonine.

2. Utilisation selon la revendication 1, dans laquelle ledit médicament est sous forme d'une unité de dosage, chaque unité de dosage comprenant une quantité de mélatonine comprise dans la gamme 0,5-50 mg.

3. Utilisation selon la revendication 1, dans laquelle ledit médicament a la forme d'une formulation pharmaceutique

qui inclut au moins un des composants additionnels suivants (α) et (β) : (α) au moins un véhicule, diluant ou adjuvant ; (β) au moins un composé anti-hypertenseur en une quantité efficace pour exercer un effet de réduction de la pression sanguine chez un patient requérant un tel traitement ; et est **caractérisé en outre par** au moins une des caractéristiques suivantes :

(i) il est adapté pour une administration orale, rectale, parentérale ou transdermique ;
(ii) il est sous forme d'unité de dosage, chaque unité de dosage comprenant une quantité de mélatonine comprise dans la gamme 2,5-20 mg ;
(iii) il est adapté pour une libération de la mélatonine à une vitesse contrôlée prédéterminée ;
(iv) il comprend aussi au moins un modificateur de récepteur de la mélatonine et/ou un modificateur du profil de mélatonine ;
(v) ledit véhicule, diluant ou adjuvant inclut au moins une résine acrylique.

4. Utilisation de mélatonine pour la fabrication d'un médicament destiné à induire chez un patient au moins un effet sélectionné parmi l'amélioration de l'humeur et de la vigilance diurne, la modification du profil de 24 heures du cortisol à la fois en réduisant le niveau moyen sur 24 heures du cortisol et en retardant le pic de niveau de cortisol sur 24 heures chez le patient, et la protection prophylactique contre l'ischémie cardiaque, le médicament étant une formulation pharmaceutique à libération contrôlée adaptée pour une administration orale, qui comprend de la mélatonine en une quantité efficace pour induire au moins un des effets mentionnés ci-dessus.

5. Utilisation selon la revendication 4, dans laquelle la formulation est **caractérisé en outre par** au moins une des caractéristiques suivantes :

(i) elle est adaptée pour libérer la mélatonine sur une période de temps prédéterminée ;
(ii) elle est adaptée pour libérer la mélatonine selon un profil qui stimule le profil plasmatique nocturne chez un humain ayant un profil endogène nocturne de mélatonine normal.

6. Utilisation selon la revendication 5, dans laquelle la formulation est sous forme particulaire comprenant des particules enrobées et les propriétés de libération contrôlées désirées sont obtenues par au moins une des caractéristiques suivantes, à savoir :

(a) par variation de la taille de particule de la mélatonine ;
(b) par utilisation d'au moins deux matériaux d'enrobage différents qui se dissolvent à des vitesses différentes dans le corps humain ;
(c) en faisant varier l'épaisseur de(s) matériau(x) d'enrobage, ce par quoi la mélatonine particulaire est enrobée avec des épaisseurs différentes de matériau(x) d'enrobage qui se dissolvent à des vitesses différentes dans le corps humain.

7. Utilisation selon la revendication 6, dans laquelle la formulation comprend de la mélatonine particulaire enrobée avec au moins un matériau d'enrobage polymérique.

8. Utilisation selon la revendication 4, dans laquelle la formulation comprend au moins un ingrédient additionnel sélectionné parmi les modificateurs de récepteur de la mélatonine et les modificateurs du profil de mélatonine.

9. Utilisation selon la revendication 8, dans laquelle la formulation comprend au moins un médicament additionnel sélectionné parmi les modificateurs benzodiazépine de récepteur de la mélatonine, les modificateurs benzodiazépine du profil de mélatonine, les bêta-bloquants, les bloqueurs de canaux calciques, et les inhibiteurs de capture de la sérotonine.

10. Utilisation de mélatonine selon la revendication 1, dans laquelle ledit patient est un patient sans baisse de pression sanguine nocturne (« non-dipper ») et/ou qui présente une élévation matinale de la pression sanguine, malgré l'utilisation de médicaments anti-hypertenseurs.

11. Utilisation selon la revendication 1, dans laquelle ledit médicament est adapté pour une administration orale, parentérale ou transdermique, et contient, dans le cas d'une administration orale, plus de 0,5 mg et pas plus de 100 mg de mélatonine, et dans le cas d'une administration parentérale ou transdermique entre 0,1 et 50 mg.

12. Utilisation selon la revendication 11, dans laquelle ledit médicament prend la forme d'une formulation qui comprend,

en plus de la mélatonine, au moins un véhicule, diluant ou adjuvant, et au moins un composé anti-hypertenseur en une quantité efficace pour exercer un effet anti-hypertenseur en présence de mélatonine, chez un patient requérant un tel traitement.